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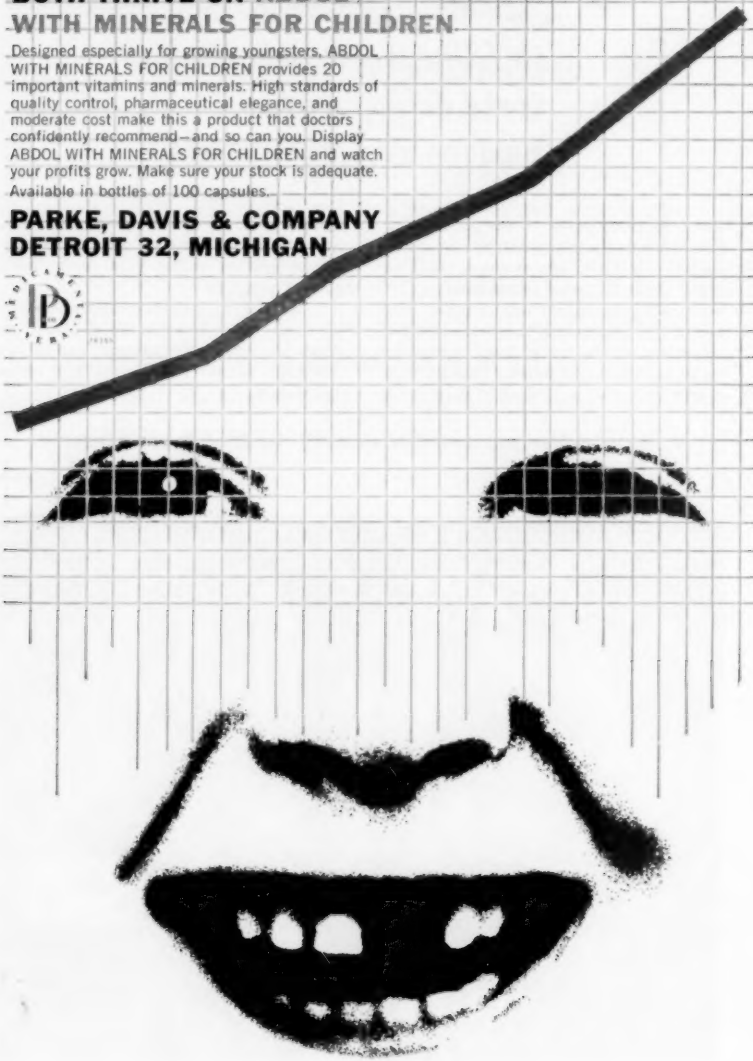

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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EDITORIAL

OUR FUTURE WORLD POSITION

A RECENT development and one which has caused some concern in the United States has been our rather considerable loss in exports in recent years and the reduction in our gold reserves. While it is true that we have the largest gold reserve of any nation in the world and our economy is strong, this trend may well be an advance warning of things to come.

Most of the great industrial nations of the world were almost completely devastated during World War II while our industrial plant grew with amazing speed and suffered not the slightest by reason of enemy attack. At the conclusion of the war, our manufactured goods were in great demand the world over since who was there to compete with us on any basis? Here, it must be said, of course, that with typical American generosity we helped rebuild the industrial machines of even our former enemies. We gave many countries economic aid albeit at the expense of increasing our national debt and mortgaging our future and that of our children. In truth, it was this willingness on our part to underwrite the recovery in many nations which saved them from disaster. This era is now past and we can see in many places in the world a rebirth of manufacturing skill and genius which in some respects is more than a match for our own. There are many products which could be mentioned with which we presently cannot compete in the world market. The truth is that, despite high tariffs, these same products are successfully competing with ours right here at home. There are many Americans who prefer foreign-made merchandise since, in many instances, it shows better workmanship, gives longer service, and in addition costs less. Already, there is a hue and cry to raise our protective tariffs still further in order more effectively to prevent competition here at home with our own industries. This, of course, can be done but it does not solve the underlying basic problem.

This country is now in some categories a "have-not" nation and this situation promises to become more acute with each passing year. There are many commodities which we must import and, in order to do this, we must export at least an equal dollar volume of goods or else be willing to continue to lose gold reserves. While it may come as a shock to many, there is no reason to expect that the dollar may not in time become "cheap" money in the world market just as other national currencies have been when their ability to compete was impaired. There is also the impact of certain economic cooperatives to be reckoned with such as those in both Western Europe and the Communist bloc of nations.

Some will argue that we need only draw within our borders and produce that needed for our own domestic consumption and everything will be fine. This just is not so. The truth is that, if we presently were not loaning other countries money to buy our goods or giving them away, our economy would be in bad straits. The Russians know this full well and they must be chortling with glee to see us faring rather badly in the world market.

We as Americans have a peculiar distaste for facing facts, particularly when these facts are unpleasant and uncomplimentary to ourselves. The fact of the matter is that we do not have a monopoly on brains and industriousness and, if anything, we have become soft, fat, and lazy in recent years by our unprecedented prosperity. The time is rapidly approaching, however, when we must realize that American supremacy has no future built-in guarantee. We will maintain our position only if we deserve it and are willing to work hard to maintain it. There are many evidences on the American scene today that make it unlikely that our rank and file will recognize the true situation. Both labor and industry are involved in this and the weakness and expediency being shown by some in government is no help. Our future survival depends in simple language on just how hard we as individuals are willing to work and just how conscientious we propose to be as compared with those in other nations. The continuing philosophy that we are the "chosen people of God carrying out some divine plan for the salvation of the world" will lead us to disaster. The question is, will we wake up to this fact in time?

L. F. Tice

DRUGS USED IN THE CONTROL OF DENTAL PAIN *

By Martin Barr **

PAIN is the most common complaint of patients to their physicians and dentists. The proper management of pain has been and will continue to be one of the most important obligations of the practitioner to his patient.

Pain

Physiologically, pain is a specific sensory experience which is mediated through nerve structures which are separate from those which mediate other sensations such as touch, pressure, heat and cold. It is composed of at least three phenomena: (1) initiation and transmission of stimuli from the periphery to the thalamus; (2) the perception of pain which is the result of the effect of the stimuli on the thalamocortical complex; and (3) the reaction to pain which is also a function of the thalamocortical complex. It is obvious, therefore, that anything which affects the thalamocortical complex might alter the sensation of, and/or the reaction to pain.

The best treatment for the relief of pain is to remove the cause. This is not always possible. Often, all that is required to remove pain are physical measures such as heat, cold and immobilization, or the use of non-narcotic analgesics such as aspirin, phenacetin, Darvon, or Zactirin. Other drugs, such as antibiotics, corticosteroids, psychotherapeutic agents, and antihistamines are valuable in the management of specific etiologic factors in the production of pain. Other than blocking or cutting nerve pathways and the use of anesthetics, procedures which are not generally desired, there remains the use of narcotic analgesics to relieve severe pain.

This paper will be limited to a brief discussion of non-narcotic and narcotic analgesics with a view toward their application in alleviating dental pain. The roles played by other therapeutic agents such

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as the corticosteroids and antihistamines, etc. in relieving pain should not be disregarded.

The Ideal Analgesic

As with any group of therapeutic agents, it is usually desirable to list the requirements of an ideal agent in a particular class. This can be done readily with the analgesic drugs.

An ideal analgesic drug should be non-addicting and free from tolerance. It should be effective orally, have a rapid onset of action, a controlled duration of effect, and an appropriate intensity of analgesia. The analgesic should act specifically on the pain centers so that an analgesic and a sedative effect may be differentiated. There should be few undesirable reactions to the drug, it should be excreted, detoxified, or eliminated without primary dependence on hepatic or similar functions for metabolic degradation. The ideal analgesic should be reversible in that a suitable antidote could stop or abolish its action.

Non-Narcotic Analgesics

Acetylsalicylic Acid (*Aspirin*)

Aspirin was first made in 1899 and its popularity as an analgesic has constantly grown. In 1958, about 10,000,000 pounds of aspirin were consumed in the United States, or enough to give a headache-relieving dose every day of the year to every adult in the country. Aspirin acts by raising the pain threshold, possibly through depression of pain centers in the thalamus.

Aspirin is absorbed from the gastrointestinal tract, peak levels being obtained in less than one hour. The acid of the stomach causes a partial hydrolysis of the ester. The ester circulates in the blood and further hydrolysis occurs in that fluid. It is thought that analgesia is associated with the presence of the acetylated molecule in the blood.

Aspirin is relatively non-toxic in average doses. Allergy to this drug does occur. Other side-effects may include sweating, thirst, nausea, vomiting, skin rashes, and tachycardia.

The usual dose of aspirin is 10 grains by mouth every 4 hours. It has been claimed that the administration of buffering agents with aspirin increases its rate of absorption and reduces the incidence of nausea and vomiting.

Combinations of aspirin with another non-narcotic analgesic such as acetophenetidin (phenacetin) and caffeine have been commonly employed for their analgesic effect. Phenacetin, like aspirin, is a salicylate, p-ethoxy acetanilid. It appears to be about as active as aspirin. Its analgesic activity is believed to be due to N-acetyl-p-aminophenol, a degradation product. Aspirin and phenacetin appear to have a synergistic action in relieving pain. The value of caffeine in such a combination is doubtful. In the treatment of headaches, caffeine probably adds to the value of the combination by dilating the cerebral blood vessels (the constriction of which may lead to headaches) and to slight cortical stimulation. There is some opinion that the use of caffeine in combinations of analgesics may actually increase dental pain due to its cortical stimulation properties. Aspirin, Phenacetin, and Caffeine Capsules and Tablets usually contain 3½ grains of aspirin, 2½ grains of phenacetin, and ½ grain of caffeine. The usual dose is 2 tablets or capsules every four hours.

Clinically, almost every ache and pain responds, to a certain extent, to aspirin. There is little doubt, however, that its analgesic effect is limited and that other agents are necessary to relieve severe pain.

Dextro Propoxyphene Hydrochloride (*Darvon—Lilly*)

Darvon is α-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride. There are four sterioisomers, of which only this one possesses analgesic activity.

Darvon is effective orally shortly after its administration. It is claimed that this compound is as effective as an analgesic, mg. for mg., to codeine and that there is no difference in the duration of action of the two drugs.

Darvon may be used in combination with aspirin and such a combination gives a greater analgesic action than either drug when used alone.

No addiction to Darvon has ever been observed. Also, such effects as nausea, vomiting, and constipation (frequently produced by opium alkaloids) have not been detected. No contraindications to the use of Darvon have been reported.

Darvon is given orally in the usual adult dosage of 32 mg. every 4 hours or 65 mg. 3 or 4 times daily, whichever is most desirable.

Darvon Compound, which is a combination of Darvon and aspirin, is usually given in a dosage of 1 or 2 capsules 3 or 4 times a day.

Darvon is available as *Pulvules "Darvon" (Lilly)* as 32 mg. and 65 mg. capsules and as *Pulvules "Darvon Compound" (Lilly)*, each containing 32 mg. Darvon, 162 mg. (2½ gr.) phenacetin, 227 mg. (3½ gr.) aspirin, and 32.4 mg. (½ gr.) caffeine.

Ethoheptazine Citrate (Zactane—Wyeth)

Ethoheptazine Citrate with Aspirin (Zactirin—Wyeth)

Ethoheptazine citrate is the newest addition to the non-narcotic analgesic armamentarium. It is chemically 4-phenyl-4-carbethoxy-N-methyl hexamethylenimine citrate. It is an unusual structure in that it has a seven-membered ring containing one nitrogen (hexamethylenimine ring).

Ethoheptazine citrate is fully effective orally within 20 minutes after its administration and its effect generally lasts 4-6 hours. It has been reported that the analgesic effect of 150 mg. of this compound is approximately equal to 30 mg. of codeine. It is used almost exclusively in combination with aspirin (Zactirin) and such a combination gives a greater analgesic effect, equivalent to 30 mg. of codeine and 10 grains of aspirin.

One of the principal indications for Zactirin is in the treatment of dental pain. It does not produce sedation, constipation, addiction or tolerance in patients as do codeine and other narcotic analgesics.

Ethoheptazine citrate is available in combination with aspirin as *Zactirin Tablets (Wyeth)*, each containing 75 mg. of ethoheptazine citrate and 5 gr. aspirin and without aspirin as *Zactane Tablets (Wyeth)*, each containing 75 mg. ethoheptazine citrate.

The usual oral dosage of Zactirin and Zactane is 1 or 2 tablets 4 times a day.

N-Acetyl-p-Aminophenol

N-acetyl-p-aminophenol is similar in its action to phenacetin. As has been explained previously, it is believed that phenacetin is broken down to N-acetyl-p-aminophenol in the body and that this substance is responsible for the analgesic activity of phenacetin.

N-acetyl-p-aminophenol is present in *Trigesic Tablets (Squibb)* together with aspirin and caffeine. The usual dosage of these tablets is 2 tablets every four hours.

Other Non-Narcotic Analgesics

There are other non-narcotic analgesics available on the market but none of these have been proven to be as valuable as those already discussed in the treatment of dental pain. Among these may be mentioned salicylamide, acetanilid, antipyrine, aminopyrine, and phenylbutazone.

Narcotic Analgesics

The narcotic or addicting analgesics fall into two classes: (1) the derivatives of opium, and (2) the "opiods" or synthetic narcotic analgesics. Members of both of these classes of analgesics have addictive properties but are useful in the treatment of severe pain. A prescriber of these drugs must possess a narcotic license.

Derivatives of Opium

Opium itself does not find much use in therapeutics today as an analgesic but the alkaloids of opium are widely employed.

Morphine (Sulfate or Hydrochloride)

Morphine produces a specific depression of the sensation of pain. It accomplishes this by a selective action on the sensory areas of the cerebral cortex.

Morphine is active when taken orally and may be considered as one of the most potent analgesics. Its duration of action is 4-5 hours. Morphine produces sedation which is useful in many instances but which is often considered an undesirable side-effect.

Morphine produces many side-effects which has limited its use in the treatment of dental pain. It markedly depresses respiration, causes constipation, nausea, and vomiting. The addiction liability to morphine is also very great.

The usual oral dose of morphine salts is 15 mg. every 4 hours as necessary. In cases of severe pain, the salt may be administered parenterally for quicker action in the same dosage.

Morphine salts are available as tablets containing 5, 8, 10, 15, and 30 mg. of salt, and as an injection containing 10, 15, 20, or 30 mg. of the salt per ml.

Dihydromorphinone Hydrochloride (Dilaudid-Knoll)

Dilaudid is about 5 times as potent an analgesic as morphine. Its duration of action is about 3 hours.

Dilaudid produces a moderate degree of sedation, not as great as that produced by morphine. It also produces a moderate amount of nausea and vomiting and marked respiratory depression. Its addiction liability is very great. It is effective in the treatment of severe pain.

The average dose of Dilaudid orally is 2.7 mg. It is available as oral tablets (2.7 mg.) for such use. It may also be administered by injection and is available in 1 ml. ampuls containing 2 or 3 mg., and in a 10 ml. multiple dose vial containing 2 mg. per ml. as the sulfate. Dilaudid is also available as 1, 2, 3, and 4 mg. tablets for hypodermic use. For those not able to swallow tablets, a suppository of Dilaudid is available for use, containing 2.7 mg. per suppository.

Methyldihydromorphinone Hydrochloride (Metopon Hydrochloride, Parke Davis)

Metopon is 2-3 times as analgesic as morphine but only half that of Dilaudid. It is milder in its sedative and side-effects than both morphine and Dilaudid. Its addiction liability is great.

Metopon is equally as effective orally as parenterally. It is useful in the treatment of moderate-severe pain.

The usual dosage of Metopon is 3-6 mg. orally. It is available as a 3 mg. capsule.

Methylmorphine (Codeine Sulfate & Phosphate)

Codeine is methylmorphine. It is usually used as the sulfate or phosphate salts.

Codeine is about 1/6th as effective an analgesic as morphine. Its duration of action is 3-4 hours. As contrasted to morphine, its sedative effect is mild.

Codeine does not produce the same degree of side effects as does morphine. It does have a moderate constipating ability. Although its addiction liability is low, addiction to codeine does occur.

The usual oral dose of codeine salts is 30 mg. every 4 hours as needed. It is effective only in the treatment of mild-moderate pain.

Codeine phosphate and sulfate are available in tablets containing 15, 30, and 60 mg. of salt.

Combinations of codeine salts with aspirin, phenacetin, and caffeine are useful in the relief of pain. *Empirin Compound with Codeine Tablets* (*Burroughs Wellcome*) are popularly employed and contain in addition to aspirin, phenacetin, and caffeine, either ⅛, ¼, ½, and 1 gr. codeine phosphate. Other popular analgesic combinations containing codeine include *Acetidine Tablets and Capsules with Codeine* (*Merck Sharp & Dohme*), ¼ and ½ gr. codeine salt per tablet or capsule, and *Trigesic Tablets with Codeine* (*Squibb*), containing ¼, ½, and 1 gr. of codeine salt per tablet.

Dihydrocodeinone Bitartrate (*Dicodid-Knoll*)

Dicodid is ½ as analgesic as morphine. It has only mild sedative action and tendencies to produce constipation, nausea, and vomiting and respiratory depression. It has a low addiction liability although greater than that for codeine. Dicodid is generally used as an antitussive and not as an analgesic.

Dihydrocodeine Bitartrate (*Rapacodin-Knoll*)

Rapacodin is ⅓-⅙ as effective an analgesic as morphine. It has only mild side-effects and sedative properties. It has a lower addicting tendency than codeine. It is effective in the relief of mild-moderate pain.

The recommended oral dosage of Rapacodin is 20 mg. repeated every four to six hours if necessary. Doses up to 60 mg. have shown rare side effects.

Rapacodin is available as 10, 20, and 40 mg. tablets; as 1 ml. ampuls containing 30 mg., and as a 20 ml. multiple dose vial containing 30 mg. alkaloidal salt per ml.

Ethylmorphine Hydrochloride (*Dionin*)

Dionin is comparable to codeine as an analgesic and also in other respects. It is seldom used systemically today and will not be discussed any further.

Pantopon (*Roche*)

Pantopon contains all of the alkaloids of opium in the same proportion in which they occur in nature, but freed from inert or irritating waxes, gums, and resins.

In most instances, ⅓ grain of Pantopon is therapeutically equivalent to ¼ grain of morphine. There is less likelihood of side reactions although there is still a high incidence of nausea produced.

The usual dosage of Pantopon is 10 to 20 mg. every 4 hours as needed orally or by injection. It is available as a 10 mg. oral tablet, as a 1 ml. ampul containing 20 mg. and as 20 mg. hypodermic tablets.

Opiod Analgesics

Levorphanol (Levo-Dromoran, Roche)

Schnider and Grüssner synthesized Levo-Dromoran in 1949. All of the analgesic activity in this compound resides in the levo-optical isomer.

Levo-Dromoran is the most potent of the current available opiods. It is 5 times more potent as an analgesic than morphine. Its duration of activity in the body is 6-8 hours.

Levo-Dromoran has a moderate sedative effect in patients. It has the ability to markedly depress respiration in substantial dosages and produces only mild constipation and infrequently nausea and vomiting. Its addiction liability is very great.

Levo-Dromoran is effective by any route of administration in the relief of severe pain. The usual dosage is 2-3 mg. orally or subcutaneously as needed.

Levo-Dromoran is available as 2 mg. oral tablets, as 1 ml. ampuls containing 2 mg., and as 10 ml. vials containing 2 mg. per ml.

Methadone Hydrochloride (Dolophine Hydrochloride, Lilly)

Methadone is a heptanone derivative and is an entirely different type of compound from morphine. It is chemically 4,4-diphenyl-6-dimethylamino-heptanone-3 hydrochloride.

Methadone is superior to codeine and meperidine as an analgesic and at least as potent as morphine. It was the first opiod to have good effectiveness when given orally. The duration of action of methadone is 4-5 hours.

Methadone has only moderate sedative action on the body but it is capable of markedly depressing respiration in high dosages. It sometimes produces constipation, nausea, and vomiting. Its addiction liability is very great.

In general, methadone is considered as being equal in potency to morphine in the relief of severe pain with less severe side-effects.

For moderate pain, 2.5 mg. of methadone given orally are usually effective for 4-6 hours. More severe pain may be controlled by oral or parenteral administration of 5 mg. doses. Very severe pain may require 10 mg.

Methadone hydrochloride is available under that name from various manufacturers and as Dolophine Hydrochloride (Lilly) as 2.5, 5, 7.5, and 10 mg. tablets; 1 ml. ampuls containing 10 mg., 20 ml. rubber-stoppered ampuls containing 10 mg. per ml., and as a syrup containing 10 mg. per 30 ml.

Meperidine Hydrochloride (Demerol, Winthrop and Breon)

Demerol is ethyl 1-methyl-4-phenylpiperidine-4-carboxylate. It is unrelated chemically to morphine. It was synthesized during a search for anti-spasmodic drugs similar to atropine. During routine tests, the compound was found to also possess analgesic properties.

Meperidine hydrochloride is $\frac{1}{10}$th as analgesic as morphine. It has a duration of action of 3-4 hours. However, it produces only very mild side effects. Meperidine does have addictive properties.

Meperidine is effective orally and parenterally for the relief of moderate to severe pain. The average dose of meperidine is 100 mg. orally or subcutaneously.

Meperidine hydrochloride is available as *Demerol (Winthrop)* as 50 and 100 mg. tablets, as an injectable of various strengths, and as an elixir containing 5 mg. per 5 ml. It is also available from Breon as 50 mg. tablets and as an injection containing 50 mg. per ml.

Recently Winthrop has made available *A. P. C. with Demerol Tablets*, each tablet containing 30 mg. of Demerol. The usual adult dose is 1 or 2 tablets, repeated if necessary, at intervals of 3-4 hours. The rationale of this combination is self-evident.

Anileridine (Leritine, Merck Sharp and Dohme)

Leritine, ethyl 1-(4'-aminophenethyl)-4-phenyl-4-carboxylate, was the first example of a synthetic narcotic drug where potency has been increased by the addition of an aminophenethyl group to a chemical structure already having analgesic properties. In Leritine, 4-aminophenethyl replaces the methyl radical of meperidine.

The potency of Leritine lies between that of meperidine and morphine, being about 2½ times that of the former and approximately ¼th that of the latter.

Leritine gives only occasional side effects and is useful in the relief of moderate to severe pain. It has great addiction liability.

The usual oral dose of Leritine is 25-50 mg., repeated every six hours if necessary. The same dosage is generally recommended for subcutaneous and intramuscular injection.

Leritine is available as 25 mg. tablets and as an injection containing 25 mg./ml. in 1, 2, and 30 ml. ampuls.

Alphaprodine Hydrochloride (Nisentil, Roche)

Nisentil, a piperidine derivative, is about ⅓ as analgesic as morphine and has a duration of action of 2-3 hours. It rarely causes sedation, nausea and vomiting, or constipation. The addiction liability to Nisentil is moderate. It is recommended for the relief of moderate to severe pain.

Nisentil is not effective when administered orally. It is usually administered intravenously if very rapid and brief analgesia is desired in a dosage of 20-30 mg. If a rapid-acting, longer-acting analgesia is desired, 30-60 mg. is usually administered subcutaneously.

Narcotic Antagonists

In recent years, several drugs have been introduced which are known as narcotic antagonists. These drugs are effective as "antidotes" in case of inadvertent overdosage, intolerance, or idiosyncrasy reactions to the narcotic drugs. In view of the fact that respiratory depression is a prime cause of death following overdosage, these drugs, which antagonize the depressing effects of the narcotics, have proven to be especially valuable antidotes.

There are two narcotic antagonists of importance in the therapeutic armamentarium, both allyl derivatives. These are *Nalline Hydrochloride (Merck Sharp & Dohme)* and *Lorfan Tartrate (Roche)*.

Nalline is available in 1 and 2 ml. ampuls, each ml. containing 5 mg. Nalline. The average dose of this antagonist is 5-10 mg. I.V. with not more than 40 mg. at one dose. Nalline is also useful as an analgesic.

Lorfan is available in 1 ml. and 10 ml. ampuls, each ml. containing 1 mg. of Lorfan. The average dosage is 1 mg. I.V. and, if required, 1 or 2 additional 0.5 mg. doses may be given.

The suggested total dosages of antagonists to be used in opiate depression in adults are shown in Table I. These ratios allow for the calculation of the total anticipated amount of antagonist to be used, when the dose of the narcotic is known.

TABLE I

SUGGESTED RATIOS BY WEIGHT OF NARCOTICS TO ANTAGONISTS

	Nalline	*Lorfan*
Narcotic	Narcotic : Nalline	Narcotic : Lorfan
Morphine	10 : 1	50 : 1
Demerol	20 : 1	80 : 1
Methadone	10 : 1	50 : 1
Nisentil	10 : 1	50 : 1
Levo-Dromoran	2 : 1	10 : 1

THE ROLE OF UNSATURATED FATS IN LOWERING SERUM CHOLESTEROL LEVELS

By Benjamin Weiss *

ALTHOUGH many factors may be involved in the pathogenesis of atherosclerosis, there are few investigators who would dismiss lipid metabolism disturbances, particularly hypercholesterolemia, as major contributors to this disease state. The consistent association of hypercholesterolemia with atherosclerosis justifies the vast amount of work being done in an attempt to elucidate the significance of the relationship and to discover practical methods of lowering elevated serum cholesterol levels. However, this approach involves two assumptions, as pointed out by Miller (1), neither of which is necessarily correct. The first is that the well-known statistical association of hypercholesterolemia and atherosclerosis is a cause-and-effect relationship, and that the severity of the atherosclerosis can be reduced by improving the lipid disorder. This seems to be a reasonable assumption, but it is by no means an established fact. The second assumption is that by improving the over-all atherosclerotic process one may prevent the appearance of that one plaque in a critical artery that produces the disabling clinical consequence. Largely on the basis of these two assumptions regarding the nature of the atherosclerotic process, a variety of agents have been introduced for the treatment of hypercholesterolemia in man.

The role of unsaturated fatty acids in human nutrition is a topic of rapidly increasing popularity in both scientific and lay publications. It has been claimed that ingestion of this group of fatty acids decreases the concentration of serum cholesterol and that an inadequate intake of certain of these acids may contribute to the elevated serum cholesterol levels so prevalent in Western civilization. Since hypercholesterolemia is allegedly involved in the pathogenesis of atherosclerosis and coronary artery disease, it has been tempting to implicate lowered intakes of unsaturated fatty acids in the rising incidence of these diseases. Although existing experimental data do not as yet warrant such conclusions, there is mounting evidence that the precise chemical

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composition of ingested fatty acids, in particular the degree of saturation, may have considerable significance in both health and disease (2). This report will be primarily concerned with a review of recent findings relative to the role of unsaturated fats in lowering serum cholesterol. However, it should be emphasized that atherosclerosis is probably not a single disease state; therefore, no one cause or treatment can be firmly established until additional basic research has been done.

On the basis of laboratory and clinical observations reported to date, an attempt will be made to answer several pertinent questions regarding the role of unsaturated fats in lipid metabolism.

1. *Will unsaturated fats effectively reduce normal and elevated serum cholesterol levels?*

A. *Animal experimentation:*

Although the effects of dietary fats in animals may differ in some respects from those in humans, the additional parameters that can be evaluated in animals make such studies worthy of exploration. Several investigators have studied the effect of various unsaturated fats in "normal" and hypercholesterolemic rats. Typical findings are those of Seskind, *et al.* (3) who reported that in the absence of cholesterol in the diet, different fat sources had no sustained effect on serum cholesterol levels. In groups fed cholesterol, the serum cholesterol levels increased most with a combination of 50% olive oil-50% palmitic acid, less with 100% olive oil, and not at all with soybean oil. The results of Avigan (4) indicate that in rats fed corn oil, or linoleic acid, the major component of corn oil, the liver cholesterol pool is greater but the serum cholesterol is, to a small but significant extent, lower than in rats receiving coconut oil.

Pollak (5) observed that, when rabbits were fed one gram of cholesterol daily for 14 days, total blood cholesterol increased sevenfold. Addition of linoleic acid (eleven parts of linoleic acid to one part ingested cholesterol) resulted in partial to complete inhibition of the hypercholesterolemia induced by cholesterol feeding. Lambert (6) showed that rabbits fed cholesterol-supplemented purified diets exhibited lower plasma cholesterol levels when safflower oil was incorporated in the diet. Similar studies performed with cholesterol-free diets indicated that rabbits fed hydrogenated coconut oil develop a more severe cholesterolemia than rabbits on safflower oil diets.

Peifer (7) reported that the metabolism of cholesterol and essential fatty acids are closely related; a high cholesterol diet accelerated essential fatty acid deficiency in rats, but addition of linoleate to the diet decreased the morbidity.

Levielle, *et al.* (8) studied the effect of dietary fat in "normal" chickens (those not receiving dietary cholesterol or other cholesterolemic agents) and found essentially no differential response to dietary fat. However, in contrast to other investigators, he found no correlation between dietary fats and plasma cholesterol when cholesterol was incorporated in the diet.

Although many experimental animals have been studied under various dietary conditions, the results appear fairly consistent. Unsaturated fats generally tend to lower high serum cholesterol levels or prevent hypercholesterolemia in cholesterol-fed animals while these fats have little or no effect on normal serum cholesterol levels.

B. *Studies in humans:*

The results in humans vary somewhat from those in animals, particularly in individuals with normal serum cholesterol levels; however, the differences are for the most part only quantitative. The majority of investigators have found that normal serum cholesterol levels are lowered when large amounts of unsaturated fats are incorporated in the diet. In one study (9), twenty-four normal persons were fed a diet containing fat of exclusively vegetable origin. The serum cholesterol levels dropped within one week, but rose again when milk fat was substituted for vegetable fat. These investigators also reported satisfactory reduction of serum cholesterol in patients with hereditary hypercholesterolemia, as well as in other subjects with elevated serum cholesterol levels, on a continuous diet of vegetable fats.

Bronte-Stewart, *et al.* (10) recorded a progressive fall in cholesterol levels after feeding control diets containing 50 grams of animal fat and then adding 100 grams of sunflower seed oil. Beveridge (11) fed his subjects a control diet containing unsaturated fatty acids as 58.5% of the total calories, and observed a steady drop in plasma cholesterol followed later by a slight rise. Following the addition of butter, there was a marked rise in plasma cholesterol. Key's group (12) found that, by substituting one ounce of sunflower seed oil for one ounce of butter fat in the diet, the blood cholesterol level could be lowered 20 mg.% per month.

The reports of Van Gasse and Miller (13) indicate a different response to unsaturated fatty acids between normal and hypercholesterolemic persons. Of the hypercholesterolemic patients studied, 80% exhibited a serum cholesterol reduction of more than 10%, whereas about 50% of persons with normal cholesterol levels showed a reduction of 10% or more. In all cases, the serum cholesterol levels promptly rose toward the base line when drug therapy was terminated. Ahrens (14) and Malmros (15) also noted a significant reduction of lipid and cholesterol levels in hypercholesterolemic patients fed diets containing artificial corn oil preparations.

Many others have also shown that the substitution of saturated fats by highly unsaturated fats in human diets, or the addition of unsaturated fats to a normal fat intake, will lower the total plasma lipids and serum cholesterol level in a high percentage of cases. The results are fairly consistent despite the varied diets and experimental conditions which have been employed.

2. *Do polyunsaturated fatty acids per se lower the serum cholesterol level as efficiently as do natural fats containing the same amounts of the same acids?*

Numerous investigators using different dietary regimens have reported that the substitution of certain types of vegetable fat for animal fat caused a decrease in plasma lipids. This may have been due to one or both of the following: (a) the presence of a factor in certain fats, mostly of vegetable origin, that actively depresses plasma cholesterol levels, or (b) the presence of a factor in certain fats, mostly of animal origin, that brings about an increase in plasma cholesterol levels. There is evidence for both of these possibilities and it is conceivable that both are partially responsible for the effects observed.

It has been shown, however, that there is no essential difference between some vegetable and animal fats in regard to effect on serum cholesterol level. Most of the vegetable oils (corn, olive, rape-seed, safflower seed, etc.) lower serum cholesterol, but coconut oil does not. Milk fat raises serum cholesterol, but whale oil depresses it. Thus, the action does not depend entirely on whether the fat is of animal or vegetable origin; rather, it appears that the cholesterol depressing effect of some oils is somehow related to the presence of varying quantities of unsaturated fatty acids.

Malmros and Wigand (16) reported on healthy subjects who were given various fats and oils as 40% of their total caloric intake. Corn and safflower seed oil had a marked depressing effect on the serum cholesterol level; rape-seed oil, a moderate effect; olive oil, a slight effect; and hydrogenated or non-hydrogenated coconut oil had no such effect. The effect of the fats on serum cholesterol was related to their content of polyunsaturated fatty acids (linoleic). Refer to Table 1. Similar results were noted with hypercholesterolemic patients.

Kinsell, *et al.* (17) found that addition to the diet of purified ethyl linoleate or trilinolein led to significant decreases in serum cholesterol in the case of a normal male subject and in patients with various disturbances in lipid metabolism.

Ahrens, *et al.* (18) have reported on the effect of hydrogenated corn oil or cottonseed oil in three subjects. In one patient, serum cholesterol was lowered from 243 to 119 mg.% by a diet containing corn oil, but the hydrogenated oils had an equal hypocholesterolemic

TABLE 1

SATURATED, UNSATURATED, AND LINOLEIC ACID COMPOSITION OF COMMON ANIMAL AND VEGETABLE FATS

	Saturated Acids	*Unsaturated Acids*	*Linoleic Acid*
	%	%	%
Safflower Oil	6.6	93.4	76.7
Sunflower Oil	7.5	92.5	63.0
Corn Oil	13.0	87.0	57.0
Soybean Oil	13.2	86.8	51.2
Cottonseed Oil	26.0	74.0	47.0
Peanut Oil	17.0	83.0	29.0
Sesame Oil	13.0	87.0	21.0
Linseed Oil	9.6	90.4	19.5
Rape-seed Oil	7.0	93.0	15.0
Olive Oil	12.0	88.0	12.0
Lard	43.0	57.0	10.0
Shortening	25.0	75.0	5.0
Coconut Oil	82.0	18.0	2.0
Butter	47.0	53.0	2.0

effect. However, in a hypercholesterolemic patient who had a plasma cholesterol of 347 mg.%, hydrogenated oil preparations led to values of 298 and 273 mg.% respectively, whereas the unmodified corn oil reduced the level to 200 mg.%. In another hypercholesterolemic patient (331-358 mg.%), hydrogenated cottonseed oil caused a decrease to 217 mg.%, whereas the native oil depressed the serum cholesterol to 177 mg.%. It may be of some importance to note that, of these three subjects, the one that exhibited equal response to hydrogenated corn oil and non-hydrogenated oil had a significantly lower serum cholesterol on the *ad libitum* diet than did the other two subjects who could certainly be classed as hypercholesterolemics. It might well be that hypercholesterolemic subjects, who presumably have a defect in lipid metabolism, respond differently to hydrogenated oils than normocholesterolemic persons. These investigators concluded that: (a) the major influence on serum-lipid levels is exerted by the glycerides, not the non-saponifiable fraction, (b) the differences in the effects of the oils tested on serum cholesterol levels are directly related to the degree of saturation of the glyceride fatty acids as measured by the iodine value of the fat, (c) the use of hydrogenated corn and cottonseed oils as sole dietary fats resulted in higher serum lipid levels than when the corresponding non-hydrogenated oils were fed. The authors admit that their results have not ruled out the possibility that the factors sought may lie in the non-glyceride fraction of the fats. However, tests performed with molecularly distilled corn oils and with reconstituted corn oil glycerides containing small amounts of non-saponifiable material suggest that, if a trace factor is involved, it must be active in extremely low concentrations.

Kinsell's results also substantiate these conclusions (19). In a group of patients fed a synthetic triglyceride as the only source of fat at an intake which provided about 2 grams of linoleic acid daily, there was a decrease in serum cholesterol levels. Hydrogenated coconut oil, which contains no essential fatty acids, caused a progressive rise in serum cholesterol levels.

In contrast, several investigators have shown that the serum cholesterol depressant effect is not entirely related to the degree of unsaturation of the fatty acids in the diet. Keys and Anderson (20) performed an elaborately controlled experiment on 24 men in which olive oil and cottonseed oil were compared. These fats were chosen because, among common food fats of vegetable origin, they have the

greatest chemical dissimilarity. No difference between the effects of these two oils on serum cholesterol concentration could be found. Armstrong, *et al.* (21) found that corn oil lowered the serum cholesterol level in humans to a greater extent than an equivalent amount of safflower seed oil, although the corn oil was more saturated and contained less linoleic acid than the safflower seed oil.

These experiments demonstrate that the non-saponifiable fraction in corn oil cannot solely account for the decrease in serum cholesterol. On the other hand, many of these investigations point to a cholesterol depressing effect of corn oil not totally accounted for by fatty acid composition.

3. *Are the changes in serum lipid levels associated with the ingestion of fats containing unsaturated acids desirable because they either prevent or improve atherosclerosis?*

Lambert (6), using rabbits, has shown that, although safflower seed oil lowered serum cholesterol level to a greater extent than hydrogenated shortening, there were only negligible differences between the oils with respect to aortic atheroma production. It was previously noted (1) that, even if there were a substantial decrease in the number and thickness of the plaques in the aorta, it is entirely possible that one tiny plaque in a critical artery could result in a severe disability. On the other hand, there have been several clinical reports which indicate that coronary patients have been benefited by a diet rich in unsaturated fats (13, 22). To date, there have not been a sufficient number of carefully controlled studies to enable formulation of specific conclusions in this respect.

4. *If so, can the desired change in the serum lipid levels be achieved by "fortification" of mixed diets, especially those containing customary amounts of animal and dairy fats?*

The results thus far indicate that a lower serum lipid level can be achieved by fortification of mixed diets. Ahrens (14) and Malmros (15), with their associates, fed diets containing artificial corn oil preparations to hypercholesterolemic patients and found a marked reduction of lipid and serum cholesterol levels. This reduction occurred without decreasing cholesterol intake and in the presence of high total fat intake. Similarly, Bronte-Stewart (10) reported that

sunflower seed oil consistently depressed serum cholesterol levels when fed alone or with a supplement of cholesterol or animal fat. However, as shown by the experiments of Keys (23), Pollak (5), and Kinsell (19), the intake of unsaturated fat must be increased if there is also a large quantity of saturated fats in the diet. Keys and his associates have found that, in regard to effect on serum cholesterol level, saturated fats are more active than are those food oils which have a neutral or opposing effect. Therefore, approximately 2 grams of linoleic acid are required to offset the hypercholesterolemic effect of 1 gram of palmitic or stearic acid. Pollak has shown that feeding of 11 parts of linoleic acid to 1 part ingested cholesterol resulted in partial to complete inhibition of the hypercholesterolemia induced in rabbits by large quantities of dietary cholesterol. It was further shown (24) that hydrogenated coconut oil as the sole fat in the diet caused a more rapid appearance of essential fatty acid deficiency symptoms in the rat than did a fat-free diet.

In summary, it appears that the inclusion in mixed diets of adequate amounts of natural fats containing 40-80% of linoleic acid will frequently lower the plasma lipid levels. The actual amount of linoleic acid required depends on the composition of the diet and the clinical status of the patient.

5. *Are diets containing large amounts of essential fatty acids better or worse than diets containing very little fat in lowering plasma lipid levels to prevent or to improve atherosclerosis?*

It has been shown in almost every instance that a low fat diet will lower serum cholesterol levels. Addition of unsaturated fats to a low-fat diet does not consistently produce further reductions in serum cholesterol levels. The observations of Keys, *et al.* (25) offer no support for the suggestion that a deficiency of essential fatty acids is responsible for the high serum cholesterol levels characterstic of populations subsisting on luxurious American and Western European diets. Effective correction of these high serum cholesterol levels involves a decrease in the relatively high concentration of saturated fats in such diets and the substitution of fats high in polyethenoid fatty acids. These investigators subsequently reported (26) no significant difference in serum cholesterol levels in patients fed two experimental fat diets, despite differences in iodine value and oleic acid content. In an epidemiologic study of various populations of the

world (27), Keys and his associates found that the characteristic serum cholesterol levels are directly related to the total consumption of fat rather than inversely related to the consumption of essential or highly unsaturated fatty acids.

The results of Horlick, *et al.* (28) indicate that the serum cholesterol is reduced about equally well by either the elimination of fat from the diet or by the ingestion of corn oil or ethyl linoleate. Ethyl linoleate did not appear to have any special depressant effect on the serum cholesterol level beyond that which could be attributed to removal of fat from the diet.

Their conclusions do not support the concept proposed by Beveridge, *et al.* (11) and Bronte-Stewart (10) that highly unsaturated fats specifically depress serum cholesterol levels. In Beveridge's experiments (11), the period of low-fat feeding which preceded the administration of corn oil was too short to eliminate the possibility that the reduction in serum cholesterol was at least partly due to the carry-over of the low-fat effect. In Bronte-Stewart's experiments (10), corn oil did not further depress the existing low serum lipid content of the Bantus, but did reduce the higher levels in Europeans. In contrast, it was shown by Kinsell, *et al.* (19) that diets rich in essential fatty acids are more effective in lowering plasma lipid levels than are low-fat diets in normal and hypercholesterolemic patients.

Although there are several reports which indicate that an equal or greater reduction in serum cholesterol is obtained with a low fat diet as compared to one high in unsaturated fats, the experiments have been performed mostly with normal individuals. Data obtained with hypercholesterolemic patients seem to indicate a greater fall in serum cholesterol when adequate amounts of unsaturated fats are incorporated in the diet. It is interesting to note that rats on fat-deficient diets developed such undesirable concurrent effects as fatty livers caused by cholesterol deposition (29).

6. *Are fatty acids more unsaturated than linoleic acid (e.g., arachidonic acid) more effective in lowering the serum cholesterol level?*

An approach to the answer of this question has been difficult because of the unavailability of purified arachidonic acid preparations. However, there is some evidence that arachidonic acid is more potent as a hypocholesterolemic agent than is linoleic acid (19). It may be the moiety responsible for the effects of unsaturated fats since it is

converted in the body from linoleic acid in the presence of pyridoxine (2). It has also been shown that linolenic acid (a tri-ene) will inhibit the deposition of cholesterol in tissue cultures of human aortic cells (30).

7. Is there any difference in the proportions of serum fatty acids between normal and atherosclerotic patients?

An attempt has been made to correlate atherosclerotic disease with a deficiency of unsaturated fatty acids or an excess of fatty acids in the serum. James, *et al.* (31) analyzed the blood lipids of 12 patients with coronary artery disease and 12 control (non-coronary) persons matched for sex and age. For the purpose of the analysis, the blood was divided into red cell, plasma phospholipid, and plasma acetone-soluble fractions. In all three fractions, the mean proportions of essential fatty acids (linoleic and arachidonic) were approximately the same in both coronary patients and controls. However, Tuna, *et al.* (32) found that the linoleic acid content of the cholesterol esters of normal plasma was higher than that of atheromatous plaques, but no qualitative or gross quantitative differences were observed. This finding has been substantiated by Hammond and Lundberg (22).

8. Is anything known concerning the mechanism by which essential fatty acids lower the serum cholesterol level?

At present, no conclusive answer can be provided to this question. However, available evidence and theories will be considered.

It is a fairly well-established fact that the endogenous synthesis of cholesterol is greater and probably more important than the quantity of exogenous cholesterol consumed (2). The reason for its accumulation, however, is less completely understood and may involve any or all of the following: (a) increased capillary fragility and permeability, (b) decreased excretion and/or increased absorption of cholesterol, (c) increased synthesis or decreased turnover of cholesterol, (d) accumulation of "unnatural" cholesterol esters which are less easily disposed of by the body.

Increased capillary fragility: Kramar and Levine (33) have found that immature albino rats fed fat-free or synthetic diets containing methyl stearate manifested pathologically low capillary resistance. However, when the same basic diet contained 57% corn oil, the

capillary resistance remained normal. They also reported that capillary resistance in humans was higher on a vegetable fat diet than on one in which the fat was exclusively of animal origin. Increased capillary fragility in essential fatty acid deficiency has also been noted by other investigators (2, 29).

Decreased excretion or increased absorption of cholesterol: Byers and Friedman (34) indicate by their data that whatever mechanism affects a reduction in serum cholesterol level of the animal fed highly unsaturated fats it does not involve an interference with the intestinal absorption of the sterol; in fact, the latter may actually be enhanced by the administration of such fats. If bile cholesterol excretion can be employed as an index of the hepatic rate of cholesterol "turnover", then it appears that a marked increase in cholesterol turnover occurs following ingestion of a highly unsaturated fat.

The increased rate of cholesterol turnover after administration of unsaturated fat is not followed by an increase in cholesterol content of the plasma, and is not always followed by an increase in the cholesterol content of the liver. This suggests that the newly formed cholesterol is being further converted to other products. In view of the fact that the principal end-products of cholesterol metabolism in the body are bile acids, there is a strong implication that the liver of the animal fed highly unsaturated fats is producing increased amounts of bile acids. This possibility has been strengthened by the finding of an increased production of bile acids after the feeding of walnut oil, and by the recent observation of increased fecal excretion of bile acids in persons fed sunflower seed oil. The latter observation suggests either that an excess of bile acids are being excreted or that lesser amounts are being reabsorbed. It therefore appears that enhanced removal of bile acid from the body provokes increased cholesterol turnover. In this connection, it is of interest to note that, when an animal is caused to excrete more bile acid, as occurs in the hyperthyroid state or when bile acid reabsorption is interfered with, serum cholesterol promptly falls. It has been suggested that a similar mechanism plays a role in the observed reduction in serum cholesterol of the subject ingesting highly unsaturated fats.

Increased synthesis of cholesterol: The data of Avigan and Steinberg (4) show that, on feeding corn oil, the over-all rate of C^{14}-labeled acetate incorporation into liver cholesterol increases, which

probably represents a net synthesis. However, if a steady state is prevailing, and this is probably a reasonable assumption in long-term experiments, the rate of excretion or breakdown of cholesterol must also be increased in corn oil-fed animals. These investigators find that, although the size of the cholesterol pool increases, the partition within this pool between plasma and liver is affected in such a way that there is less cholesterol in the blood.

Wood and Migicovsky (35), also working with C^{14}-labeled acetate, found that fatty acids inhibit cholesterol synthesis at the step where acetoacetate is formed from acetyl coenzyme-A and do so by forming a complex with a factor in the enzyme system. This complex is involved in the elongation of the carbon chain when the fatty acids are saturated and contain an even number of carbon atoms, but it has no such synthetic role when the acids are unsaturated or contain an odd number of carbon atoms in the chain. Previously, they reported that linoleic acid markedly inhibited cholesterol synthesis in rat liver homogenates (36). Later, when working with *in vivo* preparations, they found that the total cholesterol in the liver is elevated and the amount of acetate incorporated *in vivo* into liver cholesterol is increased (37).

Accumulation of "unnatural" cholesterol esters: This concept has probably been given the greatest amount of consideration (2, 18, 29, 38). Sinclair (2) suggests that cholesterol is normally esterified mainly with unsaturated fatty acids and when these are deficient in the body it is esterified with more saturated fatty acids. Therefore, abnormal esters are produced which tend to be deposited in tissues. Such deposition would be enhanced by a diet relatively high in saturated fat or high in cholesterol (which increases the dietary requirement for essential fatty acids). A diet deficient in pyridoxine or relatively low in arachidonic acid would act similarly. Hirsch (39) suggests that the unsaturated fatty acids which are normally liquid at body temperature esterify with the normally high-melting cholesterol. This liquid cholesterol ester is then kept in solution. Cholesterol esters with saturated fatty acids, on the other hand, tend to be insoluble and precipitate in the form of plaques.

Atherosclerosis might therefore be regarded as a chronic deficiency of polyunsaturated fatty acids (linoleic or arachidonic), this deficiency occurring in the body under the following conditions: (a) diets very low in essential fatty acids and adequate in other aliments,

(b) diets high in cholesterol and fairly low in essential fatty acids, (c) diets high in saturated or unnatural fats and relatively low in essential fatty acids where such fats would be acting as "antivitamins", (d) diets deficient in pyridoxine and low in arachidonic acid.

The fact that there is a wide variety of theories concerning the hypocholesterolemic action of unsaturated fats is evidence that the mechanism has, as yet, not been elucidated.

Other considerations: Although the results of various investigators have been fairly consistent despite the lack of uniformity in laboratory and clinical conditions, a significant number of differences have been observed. Possible explanations of these divergent results include the fact that conclusions have frequently been based on short-term studies and often the tests were made on only a few subjects. In some series, the data were complicated by the use of more than one fat at a time. In other experiments, the investigators used a formula or synthetic diet to avoid variation in food intake; however, such a diet does not represent the usual conditions. Another possible reason for the differences reported is given by Nichols, *et al.* (40) who conclude that changes in the serum cholesterol level are not an adequate index of the changes that occur in lipoprotein and lipid content of the serum during controlled dietary alterations. They found that the S_f 0-20 serum lipoproteins were lowered by reducing the amount of animal fat in the diet, but such vegetable fat as non-hydrogenated cottonseed oil had no such specific lowering action on the serum content of this class of lipoproteins.

Another classical problem is that of the validity of the use of laboratory animals to predict clinical responses in man. Unfortunately, the important differences between animal species in regard to the metabolism of fat and cholesterol makes it hazardous to extrapolate from such experiments to man. It is not possible to state, for example, what may be the relevance to man of the interesting observation that rabbits fed a diet high in peanut oil but low in saturated fat and devoid of cholesterol develop progressive hypercholesterolemia and, within a year, atherosclerosis. Perhaps this finding should serve as a warning against judging the ultimate cholesterogenic and atherogenic effects of diets on the basis of short-term experiments (27).

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CHEMOTHERAPEUTIC MANAGEMENT OF MYCOSIS FUNGOIDES

A Survey of 214 Cases

By John R. Sampey *

REPORTS on the chemotherapeutic management of mycosis fungoides are scattered widely through the literature. In contrast to the clinical studies in Hodgkin's disease and leukemia where single articles will describe the results with more than one hundred patients,[1] the present study covers 96 published reports which describe the therapy of only 214 cases.

From Table I it will be seen that five chemical agents account for 77% of the cases managed through chemotherapy. Nitrogen mustards dominate the field, accounting for 44% of the patients treated and 40% of the total number of remissions. Urethan and radiophosphorus are the next most frequently employed agents, and each of these shows a higher remission rate than nitrogen mustards, but the limited numbers treated reduces the significance of this statement. Preliminary results with several of the miscellaneous chemicals also give promise of further clinical trials, as may be seen in the discussion of the individual agents.

TABLE I

CHEMOTHERAPY OF 214 CASES OF MYCOSIS FUNGOIDES

Chemicals	*No. of References*	*No. of Cases*	*No. of Remissions*
N-mustards	34	94	57
Urethan	8	27	21
Radiophosphorus	12	25	18
ACTH/Cortisone	10	10	7
TEM	11	9	6
Miscellaneous	29	49	32

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Nitrogen Mustards. In 1949 Bierman reported brief improvement in 4 patients on HN2 therapy, and Gandola recorded good regression in his first attempt with this chemical. Newman described a case in which the skin cleared except for one patch and the blood and urine were normal. Schuermann obtained good palliation in 7 cases on N-mustards and urethan, and Schaefer reported the same in one case. Two of 3 cases responded clinically on HN2 for Goldberg, and one of 2 showed improvement in Roswit's investigation. Leone noted some palliation in 2 cases on HN2, and Nabarro described moderate benefit in one of 3 patients on this same chemical. Brown found no benefit in one case.

In 1950 Bauer reported good regression in 5 patients with mycosis fungoides on HN2, with 3 living at the time of reporting. Bertlich noted regressions in 6 of 8 patients, and Evans described a dramatic response in one case on mustards. Graul claimed little response in 6 of 8 patients, and he reported bad side effects with N-mustards. Leidel secured regressions with mustards and urethan in 2 patients, and Bierman noted more palliation after intra-arterial administration of the drug than by intravenous use. Foldvari reported more rapid response in 2 cases on mustards than in x-ray therapy, but the response was less durable. Reinhard noted little improvement on N-mustard therapy.

In 1951 Bertlich found 7 of 9 patients responded to HN2 therapy, and Nabarro described one fair response in 3 cases. Garcia Perez, Gardikas, Gomez and Schulze each described the palliative action of N-mustards in a case of mycosis fungoides.

In 1952 Silva and Michel noted fair response to mustard therapy in one case each of mycosis fungoides, and in 1953 Gohr found no response in a patient treated with HN2 and HN3. In 1954 Margutti described a complete cure with no relapse on R48 therapy, while Griffith recorded an excellent response in one patient on N-mustards. The next year Hammerberg experienced almost complete regression for 6 months in one patient on HN2, and Rothman employed antibiotics and HN2 for management of a case. Shimkin reported fair regressions in 9 cases treated with N-mustards, P^{32}, ACTH, etc.

In 1956 Hall found the new mustard, CB1348, less effective in 6 mycosis fungoides cases than in other lymphomas, and Bouroncle reported this compound was ineffective also in a case. DeVries noted good response in 2 patients given CB1348 in 1958.

Urethan. Attention has already been directed to the 7 regressions of mycosis fungoides on urethan and N-mustards in the report of Scheurmann and the 2 cases of Leidel. In 1949 Musso described palliation in 3 of 4 patients on urethan, and Schuermann reported an additional 2 regressions. Rehak noted good clinical and hematological remission in one case on urethan.

In 1950 Kennedy recorded clinical and histological improvement in 4 of 9 patients, and Lange observed some palliation in one case on urethan. In 1951 Leinbrock studied in detail the blood change in one case on urethan therapy, and Artunkal told of a case having a new remission 3 months after coming off the drug.

Radiophosphorus. In 1951 Margarot, Marques, and Gadrat each reported good responses in one patient on P^{32} therapy. The following year Gate observed encouraging results in 3 cases, and Larsson had regressions in 2 cases, one being extremely satisfactory. In 1953 Gate confirmed 3 good regressions, while Romieu recorded only fair response in 2 cases. In 1954 Neal treated 5 patients, 1 of whom had a complete regression, 3 good, and one slight. Zoon noted a negligible response in one case in which too little isotope was taken up by the diseased tissues. In 1955 Monacelli secured one good response, while Bazex noted little effect in one case. Diamond concluded P^{32} was ineffective in 4 cases in 1957.

TEM. Triethylene melamine gave some palliation in one of 2 patients, according to a report by Rhoads in 1950, but Karnofsky recorded no benefit in one case. The following year Karnofsky did note excellent regression in one of 2 patients on TEM. In 1952 Wright recorded one response to the drug, but Kravits and Reynaers each found one case not affected. In 1953 Karnofsky described one case with a 4 months' regression on TEM, and Romeo Orbegozo found some palliation in both Hodgkin's disease and mycosis fungoides with TEM. In 1954 Walsh recorded 2 failures on the drug, and in 1955 Wright and Arrau had one regression each.

ACTH/Cortisone. Taylor reported one good clinical response on ACTH in 1950, but he found no help in 2 cases, and Tulipan stated a negative response in one case. In 1951 Schuppli recorded some palliation in 2 cases on cortisone, but he noted some ulcer formation accompanying the therapy. Derot had one patient respond

to ACTH and antibiotics, and Essen used ACTH and cortisone to manage one case. In 1952 Reynaers found cortisone and TEM ineffective. Griffith noted partial regression in one case on ACTH in 1954, and the next year Rothman recorded improvement in a case on ACTH, HN2, and antibiotics. In 1955 Goldman obtained brief inhibition with 9-fluorohydrocortisone in one case.

Antimony. In 1949 Garb described a spectacular response of a patient on antimony potassium tartrate, and the following year he confirmed the observation. In 1950 Lincoln noted some response to tartar emetic, and Berkovsky saw good management in a case with ethylstilbamine. Lewis brought out a striking case on antimony potassium tartrate in the discussion of a paper by Roberts. In 1953 Garb published 2 more papers describing 11 cases on antimony therapy, and he found 4 good regressions to 4 years.

Radioarsenic. In 1949 Block reported negative results in one case of mycosis fungoides treated with As^{76}. In 1950 Mallet found the isotope effective in one case, and in 1952 he described the improvement of 2 more cases in the terminal stages which survived 4 and 6 months. In 1951 Marchel noted one of 2 cases had good regression on radioarsenic.

Colchicines. In 1954 Midana described histological and clinical regressions in 3 patients on colcemid therapy, and the next year Roberts reported a failure with this compound, while Ribuffo credited some response in 2 cases to colcemid.

Antibiotics. Witz concluded in 1950 that penicillin and sulfonamides were completely ineffective in 2 cases of mycosis fungoides. Cortella in 1956 described a case maintained 12 years on x-rays and actinomycin C.

6-MP. In 1954 Fountain noted regression of mycosis fungoides in one patient on 6 mercaptopurine therapy, and in 1955 he confirmed a partial remission.

FAA. Burchenal in 1949 and again in 1951 reported no response in three patients with folic acid antagonists.

TEPA. In 1953 Sykes described one good and one fair objective response to triethylene phosphoramide therapy, and in 1955 Goldman found no change in one patient given this phosphoramide.

Vitamins. In 1954 Zarafonetis recorded two cases responding to treatments with p-aminobenzoic acid, and in 1955 and 1956 Gollnick proposed new possibilities in the control of 4 cases on high dosages of B_{12} vitamin.

Radiostrontium. In 1955 Goldman induced a good response in one patient administered Sr^{90}.

Mycostatin. Jausion in 1956 obtained good regression in one case on mycostatin therapy.

Guanazolo. In 1955 Wright detected no change in one patient with mycosis fungoides treated with guanazolo.

Acknowledgments

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SELECTED ABSTRACTS

The Caries-Inhibiting Value of Stannous Fluoride in a Dentifrice. Jordan, W. A., and Peterson, J. K. *J. Am. Dent. Assoc. 58:*42 (1959). A two-year study involving 609 children, originally in the third and fourth grades, was undertaken to try to evaluate the effectiveness of 0.4 per cent stannous fluoride in a dentifrice in reducing the incidence of caries. One group of 405 children were supervised while they brushed their teeth at noon in school and were encouraged to brush their teeth after each meal at home. About one-half of these children used the dentifrice containing the stannous fluoride and one-half a dentifrice identical except for the absence of stannous fluoride. After two years, the incidence of DMF (decayed, missing, or filled) teeth was 15.8 per cent and of DMF surfaces was 20.5 per cent less in children who had used the dentifrice containing the stannous fluoride as compared with the control group. The actual DMF surface incidence mean was 3.57 for the group using the stannous fluoride and 4.49 for the control group. Statistical analysis found these results to be significant.

The authors indicated that after one year the carious surface incidence was 34 per cent less in the stannous fluoride group as compared with the control group. As stated above, this difference was 20.5 per cent after two years. The authors made no attempt to explain this apparently reduced effectiveness of stannous fluoride after a more prolonged period.

In another group of 204 children, no supervised brushing of the teeth was undertaken. The children were given the dentifrice (about one-half received the stannous fluoride dentifrice and the remainder, the control dentifrice) and urged to brush their teeth at home after each meal. The reduction in the incidence of DMF teeth was 15.9 per cent and of DMF surfaces, 12.4 per cent as compared with the control group. However, statistical analysis did not show this difference to be significant. Thus, no conclusions could be drawn with regard to the value of supervised brushing of the teeth once a day in school.

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